Complete Summary

GUIDELINE TITLE

Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines.

BIBLIOGRAPHIC SOURCE(S)

Ozer H, Armitage JO, Bennett CL, Crawford J, Demetri GD, Pizzo PA, Schiffer CA, Smith TJ, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Somerfield MR. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 2000 Oct 15;18(20):3558-85. [165 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Cancer
- Hematopoietic malignancies
- Acute Myeloid Leukemia
- Myelodysplastic Syndromes
- Neutropenic complications of cytotoxic treatments

GUIDELINE CATEGORY

Prevention
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Patients
Physicians

GUIDELINE OBJECTIVE(S)

1. To establish evidence-based clinical practice guidelines for the use of colony-stimulating factors in patients who are not enrolled in clinical trials.
2. To encourage reasonable use of hematopoietic colony-stimulating factors (colony-stimulating factors) to preserve effectiveness but discourage excess use when little marginal benefit is anticipated.

TARGET POPULATION

Adults and children with cancer undergoing cytotoxic treatment (i.e., myelosuppressive chemotherapy, myeloablative chemotherapy and bone marrow transplant).

INTERVENTIONS AND PRACTICES CONSIDERED

Administration of hematopoietic colony-stimulating factors:

Commercially available in the United States:

- Granulocyte colony-stimulating factor (G-CSF; filgrastim; Escherichia coli-derived G-CSF; Neupogen [Amgen, Thousand Oaks, CA])
- Granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim; yeast-derived GM-CSF; Leukine [Immunex, Seattle, WA])

Under development in the United States:

- GM-CSF (molgramostim; E. coli derived GM-CSF Leucomax [Schering-Plough, Madison, NJ and Sandoz, E. Hanover, NJ])

Developed primarily outside the United States:

- Lenograstim (G-CSF)
- Regramostim (GM-CSF)
- Ecogramostim (GM-CSF)

MAJOR OUTCOMES CONSIDERED

1. Duration of neutropenia
2. Incidence of febrile neutropenia
3. Incidence and duration of antibiotic use
4. Frequency and duration of hospitalization
5. Infectious mortality
6. Chemotherapy dose-intensity
7. Chemotherapy efficacy, quality of life
8. Colony-stimulating factor (CSF) toxicity

9. Economic impact.

To the extent that these data were available, the Panel placed greatest value on survival benefit, reduction in rates of febrile neutropenia, decreased hospitalization, and reduced costs. Lesser value was placed on alterations in absolute neutrophil counts.

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The original guideline was based on pertinent information from the published medical literature as of September 1993. Searches were done in Medline (National Library of Medicine, Bethesda, MD) and other databases for pertinent articles. Directed searches were made on the primary articles. The two corporations (Amgen and Immunex) with products currently on the market in the U.S. were invited to release proprietary data that would be in press before publication of these guidelines. Certain authors were also contacted to obtain additional information about trials that they had conducted. Public inquiries and comments from the American Society of Clinical Oncology (ASCO) membership were invited by notice in the ASCO News.

For the 2000 update, computerized literature searches of Medline and CancerLit were performed. The key phrases granulocyte-macrophage colony-stimulating factors, granulocyte colony-stimulating factors, and clinical trials were used in searches of the published English-language literature from 1994 to 1999.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Type of Evidence

Level

I. Evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomized, controlled clinical trial

II. Evidence obtained from at least one well-designed experimental study or low-power randomized, controlled clinical study
III. Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV. Evidence from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V. Evidence from case reports and clinical examples

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

For the 2000 update, the Guideline Update Committee had two face-to-face meetings to consider the evidence for each of the 1996 recommendations. The guideline was circulated in draft form to the update committee and to the full expert panel for review and approval.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Evidence for Recommendations

Grade

There is evidence of type I or consistent findings from multiple studies of types II, III, or IV

There is evidence of types II, III, or IV and findings are generally consistent

There is evidence of types II, III, or IV but findings are inconsistent

There is little or no systematic empirical evidence

COST ANALYSIS

Impact of Colony-Stimulating Factors (CSFs) on Economics of Febrile Neutropenia

The routine use of CSFs for primary prophylaxis cannot be justified on the basis of cost savings with any routine chemotherapy. Cost analyses have shown that CSFs save money when the risk of febrile neutropenia (FN) is greater than 40%, but no routine regimens have rates greater than 15%. This analysis was sometimes confused with the initial CSF guideline that used a 40% rate of FN as a clinical threshold for use of CSFs, based on the observed rate of neutropenia seen in the initial randomized trials used for Food and Drug Administration licensing in the United States.

The economic models used costs of hospitalization for FN of $10,000; if the costs were much lower, as with early-discharge models or outpatient treatment models, the rate of FN would have to be much higher to offset the costs of using CSFs. Alternatively, CSFs could be justified if they cost substantially less. The use of CSFs at a much lower dose (e.g., 2 microgram/kg instead of 5 microgram/kg), which is promising but needs confirmation, would lower the cost.

For secondary prophylaxis, the rate of FN could be 40% and could justify use of CSF, but dose modification would be a medically acceptable alternative because no major clinical benefit of maintaining delivery of previously toxic levels of chemotherapy with CSF use has been shown. A recent decision analysis model showed acceptable cost-effectiveness of CSFs to maintain dose-intensity in adjuvant therapy for breast cancer, but CSFs are rarely needed for four cycles of doxorubicin and cyclophosphamide, and no benefit has been found to date even for escalated doses of doxorubicin with CSF support.

A major advance would be a model to predict who will develop FN, so that CSF use could be restricted to that group. At present, it is not possible to predict who will develop FN and who would therefore benefit from prophylaxis with CSFs. Current models are promising but need prospective validation. Some possible predictors include a high risk of FN of 49% (23 of 47 patients) if the absolute lymphocyte count is less than 700/mm^3, compared with 11% (seven of 65 patients) if the absolute lymphocyte count is greater than 700/mm^3. Similarly, others have proposed that the risk of FN is higher in adjuvant breast cancer chemotherapy if the hemoglobin or absolute neutrophil count (ANC) falls during the first cycle of chemotherapy.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were circulated in draft form, and all [committee] members had an opportunity to comment on the levels of evidence and the systematic grading of the data supporting each recommendation.

The content of the guidelines and the manuscript were reviewed and approved by the American Society of Clinical Oncology (ASCO) Health Services Research Committee and by the ASCO Board before dissemination. In addition, several practitioners among the ASCO membership who had not been directly involved in development of the guidelines were asked to assess the clarity and utility of the document.

Guidelines were validated by comparing them with recommendations for colony-stimulating factor (CSF) use developed in other countries and by several academic institutions.

For the 2000 update, the guideline was circulated in draft form to the update committee and to the full expert panel for review and approval.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The American Society of Clinical Oncology (ASCO) has recently updated its 1996 recommendations for the use of hematopoietic colony-stimulating factors (Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. J Clin Oncol, 14(6), 1996: 1957-1960). Each recommendation from the 1996 guideline is listed below. Unless otherwise indicated, the 1996 guideline remains unchanged based on a review of the most recent evidence. For those recommendations that have changed in the 2000 update, both the original recommendation and the 2000 update are presented.

1. Guidelines for Primary Prophylactic Colony-Stimulating Factor Administration

   General Circumstances

   Primary administration of colony-stimulating factors (CSFs) was shown to reduce the incidence of febrile neutropenia by approximately 50% in the three major randomized trials in adults in which the incidence of febrile neutropenia was greater than 40% in the control group. The value of primary colony-stimulating factor administration has not been clearly established in less myelosuppressive regimens. It is recommended that primary administration of colony-stimulating factors be reserved for patients expected to experience levels of febrile neutropenia comparable to or greater than those observed in control patients in these randomized trials, i.e., an expected incidence $\geq$40%. Thus, in general, for previously untreated patients receiving most chemotherapy regimens, primary administration of colony-stimulating factors should not be used routinely.

   Specific Circumstances

   Clinicians may occasionally be faced with patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for febrile neutropenia or infection because of bone marrow compromise or comorbidity. It is possible that primary colony-stimulating factor administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive. Such risk factors might include the following: pre-existing neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing

large amounts of bone marrow; a history of recurrent febrile neutropenia while receiving earlier chemotherapy of similar or lesser dose-intensity; or conditions potentially enhancing the risk of serious infection, e.g., poor performance status and more advanced cancer, decreased immune function, open wounds, or already-active tissue infections. This is not meant to be an all-inclusive list; it is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of a colony-stimulating factor will be appropriate outside of uses recommended in other guidelines.

2. Guidelines for Secondary Prophylactic Colony-Stimulating Factor Administration

   There is evidence that colony-stimulating factor administration can decrease the probability of febrile neutropenia in subsequent cycles of chemotherapy after a documented occurrence in an earlier cycle. Even if febrile neutropenia has not occurred, the use of colony-stimulating factors may be considered if prolonged neutropenia is causing excessive dose reduction or delay in chemotherapy. However, in the absence of clinical data supporting maintenance of chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of CSFs.

   2000 Recommendation: In the setting of many tumors exclusive of curable tumors (e.g., germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as a primary therapeutic option. No published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction after neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment.

3. Guidelines for Colony-Stimulating Factor Therapy

   Afebrile Patients:

   There are inadequate data to know whether or not patients with neutropenia but no fever will benefit clinically from the initiation of a colony-stimulating factor at the time neutropenia is diagnosed; intervention with a colony-stimulating factor in afebrile neutropenic patients is not recommended.

   2000 Recommendation: Current evidence supports the recommendation that colony-stimulating factors should not be routinely used for patients with neutropenia who are afebrile. The strength of this recommendation has increased with a trial reported in 1997 (Hartmann et al., 1997).

   Febrile Patients:

   For the majority of patients with febrile neutropenia, the available data do not clearly support the routine initiation of colony-stimulating factors as adjuncts to antibiotic therapy. However, certain febrile, neutropenic patients may have

prognostic factors that are predictive of clinical deterioration, such as pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), or fungal infection. The use of colony-stimulating factors together with antibiotics may be reasonable in such high-risk patients, even though the benefits of administration under these circumstances have not been definitively proved.

2000 Recommendation: The collective results of eight trials (Maher et al., 1994; Mitchell et al., 1997; Vellenga et al., 1996; Anaisse et al., 1996; Mayordomo et al., 1995; Ravaud et al., 1998; Riikonen et al., 1994; Biesma et al., 1990) provide strong and consistent support for the recommendation that colony-stimulating factors should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows: fever of $\leq$ 10 days in duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection; and no uncontrolled malignancies. The eight trials have consistently shown a decrease in the duration of neutropenia of less than 500/microliters, but clinical benefit has not consistently accompanied the decreased duration of neutropenia.

Certain patients with fever and neutropenia are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of a colony-stimulating factor for such high-risk patients may be considered, but the benefits of a colony-stimulating factor in these circumstances have not been proven. These factors include profound (absolute neutrophil count <100/microliters) neutropenia, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), and invasive fungal infection. Age greater than 65 years and post treatment lymphopenia may also be high-risk factors but have not been consistently confirmed by multicenter trials.

4. Guidelines for Use of Colony-Stimulating Factors to Increase Chemotherapy Dose-Intensity

Outside of clinical research trials, there is little justification for the use of colony-stimulating factors to increase chemotherapy dose-intensity. In settings where clinical research demonstrates that dose-intensive therapy not requiring progenitor-cell support produces improvement in disease control, colony-stimulating factors should be used when these therapies are expected to produce significant rates of febrile neutropenia (e.g., in $\geq$40% of patients).

2000 Recommendation: In the absence of more trials demonstrating a favorable effect on overall survival, disease-free survival, quality of life, or toxicity, there is no justification for the use of colony-stimulating factors to increase chemotherapy dose-intensity or schedule or both outside of a clinical trial. This application of colony-stimulating factors use remains the domain of appropriately designed clinical investigation.

5. Guidelines for Use of Colony-Stimulating Factors as Adjuncts to Progenitor-Cell Transplantation

Colony-stimulating factors can successfully shorten the period of neutropenia and reduce infectious complications in patients undergoing high-dose cytotoxic therapy with autologous bone marrow transplantation. Colony-stimulating factors are effective in mobilizing autologous peripheral blood progenitor cells for transplantation, and autologous peripheral blood progenitor cell transplantation has been shown to lead to earlier hematopoietic recovery than autologous bone marrow transplantation (Beyer et al., 1995; Schmitz et al., 1996). Trials have demonstrated the value of colony-stimulating factor administration after high-dose chemotherapy and peripheral blood progenitor cell transplantation (Nademanee et al., 1994; Schmitz et al., 1995; Klumpp et al., 1995). Available data suggest clinical benefits after allogeneic bone marrow transplantation, and routine primary colony-stimulating factor administration in this setting appears warranted (Nemunaitis et al., 1995). Colony-stimulating factors can also be used to mobilize donor peripheral blood progenitor cells for allogeneic transplantation (Korbling et al., 1995; Dreger et al., 1994; Schmitz et al., 1995; Bensinger et al., 1995). There also may be a role for the colony-stimulating factors in assisting in the recovery of patients who experience delayed or inadequate neutrophil engraftment following progenitor-cell transplantation.

Colony-stimulating factors can be routinely recommended as adjuncts to allogeneic and autologous progenitor cell transplantation, both for mobilization of peripheral blood progenitor cells and as a means to speed hematopoietic reconstitution following bone marrow transplantation or peripheral blood progenitor cell transplantation. Administration of a colony-stimulating factor in cases of engraftment failure is warranted.

2000 Recommendation: Colony-stimulating factors are recommended to help mobilize peripheral blood progenitor cells and after peripheral blood progenitor cell infusion. Mobilized peripheral blood progenitor cells have largely replaced bone marrow-derived cells for use in autologous transplantation. Side effects associated with mobilization and subsequent apheresis are usually limited and include constitutional symptoms and a decrease in platelets and other hematopoietic elements, especially after mobilization with combination of chemotherapeutic agents and a colony-stimulating factor. The optimal dose of granulocyte colony-stimulating factor in the setting of mobilization may yield greater content of CD34+ progenitor cells in peripheral blood progenitor cell product, as documented in patients with hematologic malignancies and in patients with rheumatoid arthritis (Nademanee et al., 1994; Snowden et al., 1998). Although the optimal method of mobilization needs further investigation, especially in heavily pretreated patients, administration of granulocyte colony-stimulating factor, either alone or in combination with granulocyte-macrophage colony-stimulating factor, or after the use of chemotherapeutic agents, generates peripheral blood progenitor cells, leading to rapid hematopoietic recovery, shorter hospitalization, and possibly reduced costs (Schmitz et al., 1996; Ho et al., 1996; Meisenberg et al., 1998; Cesana et al., 1998). Further investigations are necessary to assess the potential risks, especially that of secondary hematologic malignancies associated with the use of combining chemotherapeutic agents and colony-stimulating factors (Krishnan et al., 2000). The role of colony-stimulating factor mobilized donor bone marrow in

the autologous transplant setting is also under assessment (Weisdorf et al., 1997).

6. Guidelines for Use of Colony-Stimulating Factors in Patients With Acute Leukemia and Myelodysplastic Syndromes

Acute Myeloid Leukemia:

There is evidence from several studies, most conducted in older patients, that colony-stimulating factor administration can achieve modest decreases in the duration of neutropenia, accompanied in some but not all studies by an amelioration of infectious complications, when begun shortly after the completion of acute myeloid leukemia induction therapy. There has been no consistent improvement in complete response rates, and long-term outcome at 2 years. There does not appear to be any harm from colony-stimulating factor administration when given after completion of induction chemotherapy. Primary administration of a colony-stimulating factor can be used after completion of induction chemotherapy in patients >55 years of age. Although there are fewer data, it is likely that the results showing shortening of the duration of neutropenia may apply to younger patients as well. Colony-stimulating factors given either before and/or concurrently with chemotherapy for priming effects still cannot be recommended outside of a clinical trial.

2000 Recommendation: Colony-stimulating factor use can be considered in this setting if benefits in terms of possible shortening of hospitalization outweigh the costs of colony-stimulating factor use. Several studies have shown that colony-stimulating factor administration can produce modest decrease in the duration of neutropenia when begun shortly after completion of the initial days of chemotherapy of the initial or repeat induction. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest, although patients 55 years of age or older are most likely to benefit from colony-stimulating factor use. No study has yet demonstrated significant improvement in complete response rates or long-term outcome. Thus, while there seems to be minimal risk associated with the use of colony-stimulating factors in this situation, the choice of whether or not to use the colony-stimulating factor is likely to be determined by cost considerations. In a nutshell, the cost of the cytokine must be balanced against any possible shortening of hospitalization associated with the slightly more rapid marrow recovery, as, for example, in patients 55 years of age or older. It is not known from the published data whether the colony-stimulating factors significantly accelerate recovery to absolute neutrophil counts of 100 to 200/mm^3. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from hospital.

There is no evidence that colony-stimulating factors given either before or concurrently with chemotherapy for priming effects are of benefit, and their use in this fashion cannot be recommended outside the setting of the clinical trial.

There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with acute myeloid leukemia in

remission. Although the randomized studies did not address this issue, it is likely that this will be associated with decreased rates of hospitalization and possibly shorter durations of hospitalization in such patients. No benefit has been demonstrated in terms of prolongation of complete response duration of overall survival; however, the available evidence indicates that the colony-stimulating factors can be recommended after the completion of consolidation chemotherapy.

Myelodysplastic Syndromes:

Colony-stimulating factor can increase the absolute neutrophil count in neutropenic patients with myelodysplastic syndromes. Data supporting the routine long-term continuous use of colony-stimulating factors in these patients are lacking. Intermittent administration of colony-stimulating factors may be considered in a subset of patients with severe neutropenia and recurrent infection.

Acute Lymphoblastic Leukemia [Note: this topic is new to the 2000 updated guideline]

2000 Recommendation: The data are sufficient to recommend granulocyte-colony-stimulating factor administration begun after completion of the first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of less than 1,000/mm^3 by approximately 1 week. Effects on the incidence and duration of hospitalization and the acquisition of serious infections are less consistent. Although there was a trend for improved complete response rates in one large study (Larson et al., 1998), particularly in older adults, there was no prolongation of disease-free or overall survival in any of the trials. Granulocyte- colony-stimulating factor can be given together with the continued corticosteroid/antimetabolite therapy, which is a feature of many acute lymphoblastic leukemia regimens, without evidence that such concurrent therapy prolongs the myelosuppressive effects of chemotherapy. As in acute myeloid leukemia, it is not known from the published data whether the colony-stimulating factors significantly accelerate recovery to absolute neutrophil counts of 100 to 200/mm^3. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from the hospital. The use of granulocyte- colony-stimulating factor for children with acute lymphoblastic leukemia was associated with small benefits in days of antibiotic use or in-hospital days, although a small amount of additional costs was incurred, after the costs of the colony-stimulating factors were taken into consideration. Cost estimates of colony-stimulating factors for adults with acute lymphoblastic leukemia have not been reported.

Leukemia in Relapse [Note: this topic is new to the 2000 updated guideline]

2000 Recommendation: The available data are not sufficient to recommend either for or against the use of colony-stimulating factors in patients with refractory or relapsed acute lymphoblastic leukemia. Few controlled studies have evaluated colony-stimulating factors in patients with relapsed or

refractory acute leukemia. The available data suggest shortening of the duration of neutropenia but are inadequate to comment on any effects of infectious complications and, in particular, on whether there may be an adverse effect on response rates in some patients with myeloid malignancies because of a stimulatory effect on leukemia growth in a situation in which there is less of a guarantee that chemotherapy will produce sufficient cytoreduction. Therefore, there is no evidence that colony-stimulating factor are of important benefit in patients with refractory or relapsed myeloid leukemia, and they should be used judiciously or not at all in such patients.

7. Guidelines for Use of Colony-Stimulating Factors in Patients Receiving Concurrent Chemotherapy and Irradiation

   Colony-stimulating factors should be avoided in patients receiving concomitant chemotherapy and radiation therapy.

   2000 Recommendation: Colony-stimulating factor should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, in patients receiving radiation therapy involving large fields, therapeutic use of colony-stimulating factors may be considered if prolonged delays secondary to neutropenia are expected.

8. Guidelines for Use of Colony-Stimulating Factors in the Pediatric Population

   In the absence of conclusive pediatric data, the guidelines recommended for adults are generally applicable to the pediatric age group. However, optimal colony-stimulating factor doses have yet to be determined. Further clinical research into the use of these factors in support of chemotherapy and progenitor-cell transplantation in the pediatric age group should be given high priority.

9. Guidelines for Colony-Stimulating Factor Dosing and Route of Administration

   In adults, the recommended colony-stimulating factor doses are 5 micrograms/kg/d of granulocyte colony-stimulating factor (filgrastim) or 250 micrograms/m^2/d of granulocyte-macrophage colony-stimulating factor (sargramostim). These agents can be administered subcutaneously or intravenously as clinically indicated. Colony-stimulating factor dose escalation is not advised. The available data suggest that rounding the dose to the nearest vial size may enhance patient convenience and reduce costs without clinical detriment.

   2000 Recommendation: In adults, the recommended colony-stimulating factor doses are 5 micrograms/kg/d for granulocyte-colony-stimulating factor (filgrastim) and 250 micrograms/m^2/d for granulocyte-macrophage-colony-stimulating factor (sargramostim) for all clinical settings other than peripheral blood progenitor cell mobilization. In the setting of peripheral blood progenitor cell mobilization, if granulocyte-colony-stimulating factor is used, a dose of 10 micrograms/kg/d seems preferable. Outside of this indication,

colony-stimulating factor dose escalation is not advised. Rounding the dose to the nearest vial size is an appropriate strategy to maximize cost benefit. The preferred route of colony-stimulating factor administration is subcutaneous.

10. Guidelines for Initiation and Duration of Colony-Stimulating Factor Administration

    Existing clinical data suggest that starting granulocyte- or granulocyte-macrophage- colony-stimulating factor between 24 and 72 hours subsequent to chemotherapy may provide optimal neutrophil recovery. Continuing the colony-stimulating factor until the occurrence of an absolute neutrophil count of 10,000/microliters after the neutrophil nadir, as specified in the granulocye- colony-stimulating factor package insert, is known to be safe and effective. However, a shorter duration of administration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.

    2000 Recommendation: The optimal timing and duration of colony-stimulating factor administration are still under investigation. Starting colony-stimulating factors up to 5 days after peripheral blood progenitor cell reinfusion is reasonable based on available clinical data.

11. Special Commentary on Comparative Clinical Activity of Granulocyte-Colony-Stimulating Factor and Granulocyte Macrophage-Colony-Stimulating Factor

    Guidelines about equivalency of the available recombinant preparations of granulocyte- colony-stimulating factor and granulocyte macrophage- colony-stimulating factor cannot be proposed because there have been no large-scale, prospective, comparative trials evaluating relative colony-stimulating factor efficacy. The strength of evidence to support the use of granulocyte-colony-stimulating factor or granulocyte macrophage- colony-stimulating factor varies based on the specific indication for colony-stimulating factor administration, e.g., support after bone marrow transplantation or use with nontransplantation chemotherapy regimens. The Panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost-effectiveness.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is discussed with each recommendation (see Major Recommendations).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

1. Appropriate clinical utilization of colony-stimulating factors: The guideline encourages reasonable use of colony-stimulating factors to preserve effectiveness but discourages excess use when little marginal benefit is anticipated.
2. Improved clinical outcomes: Avoiding the occurrence of febrile neutropenia by use of a colony-stimulating factor might be expected to enhance patient quality of life, reduce hospital costs, and improve chemotherapy delivery.

Subgroups Most Likely to Benefit:

In three randomized controlled trials with adults, primary administration of colony-stimulating factor has been effective in reducing the incidence of febrile neutropenia in patient groups with an incidence of febrile neutropenia of $\geq$40%.

POTENTIAL HARMS

1. Granulocyte-Colony-Stimulating Factor (Filgrastim): The predominant side effect associated with administration of granulocyte- colony-stimulating factor has been medullary bone pain. In randomized trials, 15% to 39% of patients receiving approximately 5 Âµg/kg/d have described this symptom, compared with a 0% to 21% incidence in control patients. Less frequent side effects reported include exacerbations of preexisting inflammatory conditions, e.g., eczema, psoriasis, or vasculitis; rashes; allergic reactions; acute febrile neutrophilic dermatosis (Sweet syndrome); transient leukemia cutis, injection site reactions; mild alopecia; splenomegaly; splenic infarction; moderate reductions in platelet counts; Other laboratory abnormalities have included elevations in lactate dehydrogenase, uric acid, and serum and leukocyte alkaline phosphatase, presumably due to enhanced myeloid cell turnover.
2. Granulocyte Macrophage-Colony-Stimulating Factor (Sargramostim): Patients who do have side effects most commonly experience fever, nausea, fatigue, headache, bone pain, chills, myalgias, and injection site reactions. Other potential toxicities observed include diarrhea, anorexia, arthralgias, skin rashes, facial flushing, capillary leak, dyspnea, thrombotic events, hypotension, and conjunctivitis. Peripheral blood alterations can include subclinical thrombocytopenia and elevations in blood levels of monocytes, basophils, and especially eosinophils. Similar to the effects seen with granulocyte- colony-stimulating factor, granulocyte macrophage- colony-stimulating factor has caused reversible increases in serum lactate dehydrogenase, alkaline phosphatase, and uric acid. Decreases in serum cholesterol and albumin. Have also been observed.
3. Granulocyte Macrophage-Colony-Stimulating Factor (Molgramostim): Patients receiving molgramostim at doses of 5 to 20 Âµg/kg have experienced injection site reactions, rash, pruritus, fever, edema, fatigue, paresthesias, anorexia, diarrhea, myalgias, and bone pain. It has been harder to clearly

identify granulocyte macrophage- colony-stimulating factor--associated toxicities in placebo-controlled studies. More serious reactions have included pericarditis, atrial fibrillation, pleural effusion, thrombotic events, and capillary leak, as well as changes in blood counts and serum chemistries comparable to those seen with very high sargramostim doses. It is not clear whether the side effects of granulocyte- colony-stimulating factor and granulocyte macrophage- colony-stimulating factor differ markedly when conventional colony-stimulating factor doses are administered.

4. Colony-Stimulating Factors as an adjunct to progenitor cell transplantation: Side effects associated with colony-stimulating factor-mobilized peripheral blood progenitor cells and subsequent apheresis are usually limited and include constitutional symptoms and a decrease in platelets and other hematopoietic elements.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

1. Guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonable directed at obtaining the same results. Accordingly, the American Society of Clinical Oncology (ASCO) considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative drug applications and novel approaches to the treatment of disease.
2. Clinicians may occasionally be faced with patients who might benefit from a relatively nonmyelosuppressive chemotherapy but have potential risk factors for febrile neutropenia or infection because of bone marrow compromise or comorbidity. It is possible that primary colony-stimulating factor administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications even though the data supporting such use is not conclusive. Such risk factors might include preexisting neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; a history of recurrent febrile neutropenia while receiving earlier chemotherapy of similar or lesser dose-intensity; or conditions potentially enhancing the risk of serious infection, e.g., decreased immune function, open wounds, or already active tissue infections. This is not meant to be an all-inclusive list; it is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of a colony-stimulating factor will be appropriate outside of uses recommended in other guidelines.
3. Guidelines about equivalency of the available recombinant preparations of granulocyte- colony-stimulating factor and granulocyte macrophage-colony-stimulating factor cannot be proposed because there have been no large-scale, prospective, comparative trials evaluating relative colony-stimulating

factor efficacy. The strength of evidence to support the use of granulocyte-colony-stimulating factor or granulocyte macrophage- colony-stimulating factor varies based on the specific indication for colony-stimulating factor administration, e.g., support after bone marrow transplantation or use with nontransplantation chemotherapy regimens. The Panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost-effectiveness.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Ozer H, Armitage JO, Bennett CL, Crawford J, Demetri GD, Pizzo PA, Schiffer CA, Smith TJ, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Somerfield MR. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 2000 Oct 15;18(20):3558-85. [165 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1994 Nov (updated 2000)

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology (ASCO)

GUIDELINE COMMITTEE

American Society of Clinical Oncology (ASCO) Ad Hoc Colony-Stimulating Factor Guideline Expert Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The Panel was composed of experts in clinical medicine, clinical research, colony-stimulating factor (CSF) use, bone marrow transplantation (BMT), infectious diseases, basic research, biostatistics, medical economics, and medical decision-making.

Names of Committee Members: James R. Anderson, PhD; Paul N. Anderson, MD; James O. Armitage, MD; Stacey Beckhardt; Charles L. Bennett, MD; Gerald P. Bodey, MD; Jeffrey Crawford, MD; Nancy E. Davidson, MD; George D. Demetri, MD; John T. Hamm, MD; Bruce Hillner, MD; Carl G. Kardinal, MD; Mark N. Levine, MD; John A. Miller, MD; Langdon L. Miller, MD; Judith J. Ochs, MD; Howard Ozer, MD, PhD; Victor M. Santana, MD; Charles A. Schiffer, MD; Thomas C. Shea, MD; Thomas J. Smith, MD; Saroj Vadhan-Raj, MD; James L. Wade III, MD; Jane C. Weeks, MD; Rodger J. Winn, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All participants in the guideline development process complied with American Society of Clinical Oncology (ASCO) policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel, the Health Services Research Committee, and the Board of Directors, as well as the ASCO reviewers, completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The substance of any positive response was shared through oral reports at each meeting of the relevant group. The Panel, Committee, and Board made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. One member of the Health Service Research Committee who had stock ownership in a company with a commercial interest in colony-stimulating factor (CSF) development was prohibited from voting, but was allowed to participate in deliberations.

GUIDELINE STATUS

This is the current release of the guideline.

To date, three updates have been issued:

1. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 2000 Oct;15(18):3558-85.
2. 1997 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1997 Oct;15(10):3288.
3. Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. J Clin Oncol 1996 Jun;14(6):1957-60.

American Society of Clinical Oncology (ASCO) guidelines are updated annually by a Review Committee of the full Guidelines Expert Panel, and every 3 years by the full Panel.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society for Clinical Oncology (ASCO) Web site.

Previous versions of the guideline are available from the American Society of Clinical Oncology (ASCO) Web site:

- 1996 Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors.
- Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Practice Guidelines.

Print copies: Available from American Society for Clinical Oncology, 1900 Duke Street, Suite 200, Alexandria, VA 22314; guideline@asco.org

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Bennett CL, Weeks JA, Somerfield MR, Feinglass J, Smith TJ. Use of hematopoietic colony-stimulating factors: comparison of the 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines. Health Services Research Committee of the American Society of Clinical Oncology. J Clin Oncol 1999 Nov;17(11):3676-81.

Print copies: Available from ASCO, 1900 Duke Street, Suite 200, Alexandria, VA 22314; guideline@asco.org

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on September 1, 1998. It was verified by the guideline developer on December 1, 1998.

This summary was most recently updated by ECRI on December 1, 2000, to reflect the information published in the 2000 update of the original guideline (2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 2000 Oct;15[18]:3558-85). The updated information was verified by the guideline developer as of December 20, 2000.

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